09/445865

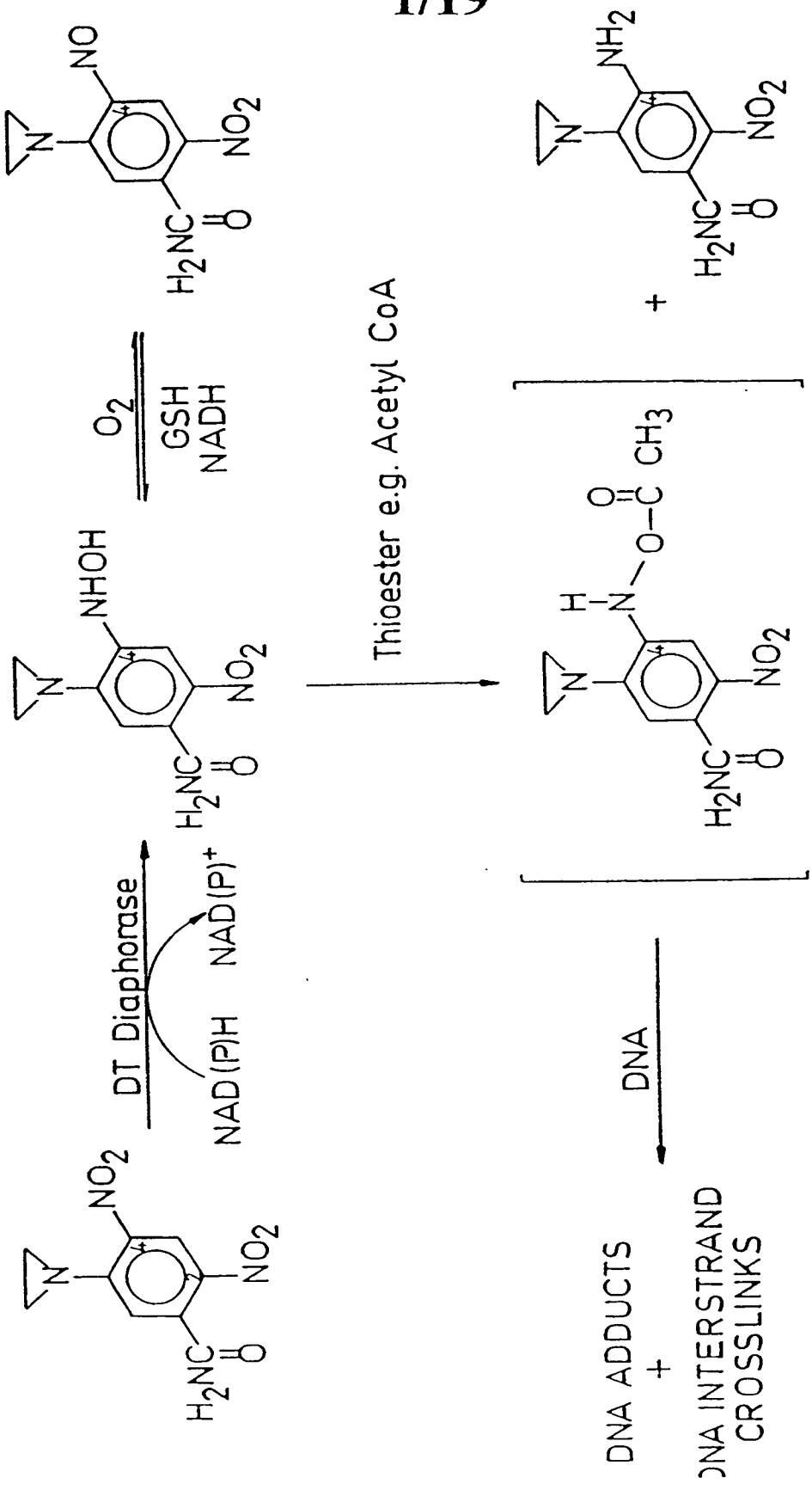
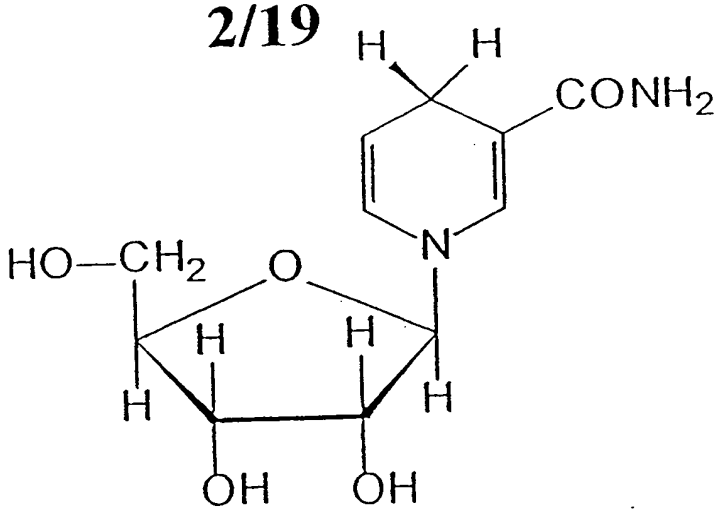


Fig. 1



$C_{11}H_{16}N_2O_5$
256.25
256.105921
C 51.6% H 6.3% N 10.9% O 31.2%

Fig. 2

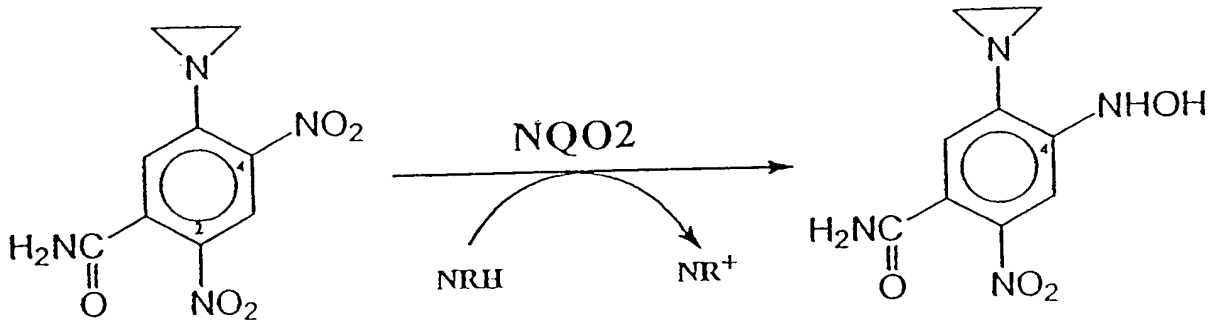


Fig. 3

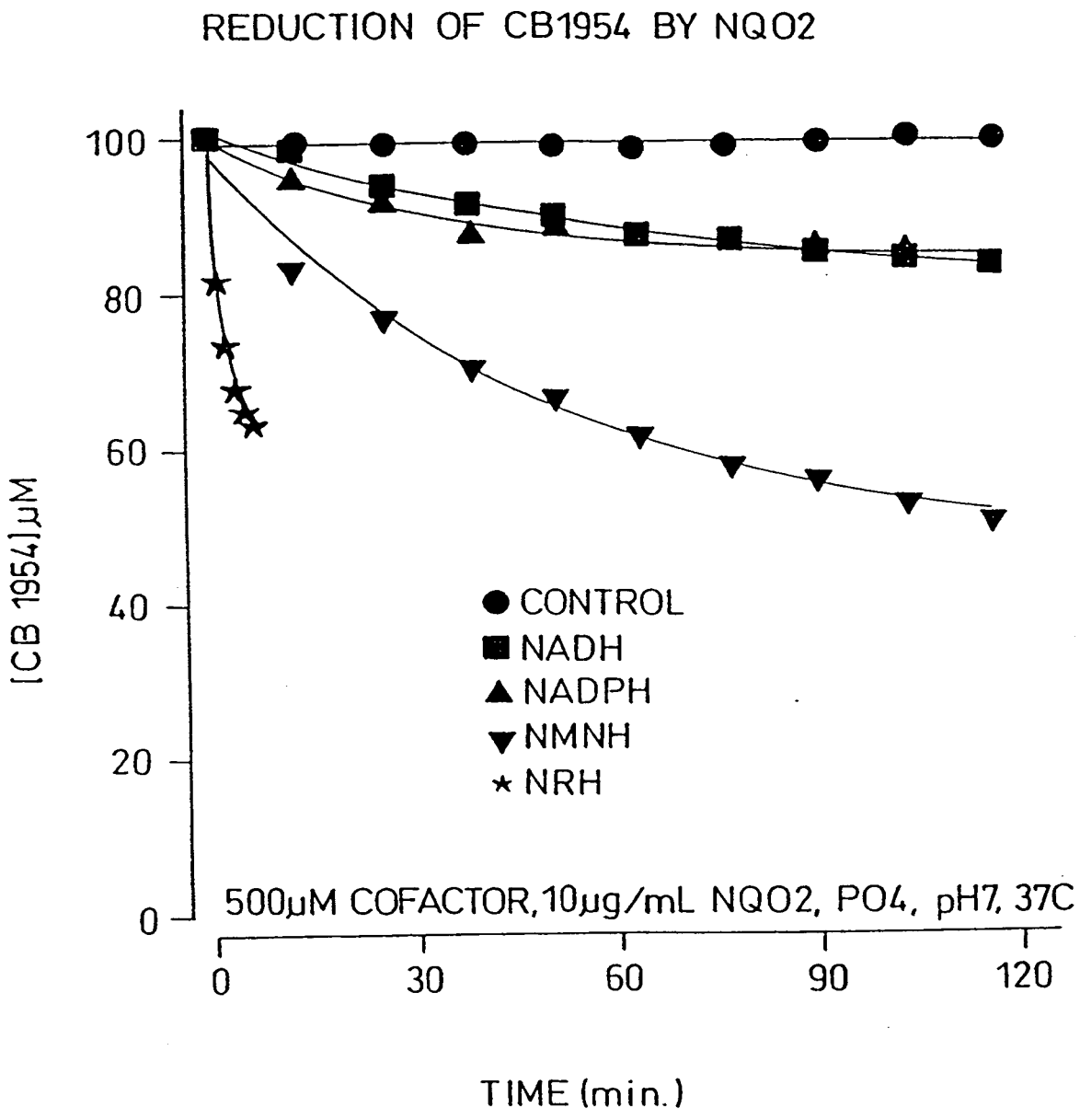

REDUCTION OF CB1954 BY NQO2
100
80
60
40
20
0
[CB 1954]µM
CONTROL
NADH
NADPH
NMNH
NRH
500µM COFACTOR, 10µg/mL NQO2, PO4, pH7, 37C
0
30
60
90
120
TIME (min.)

Fig. 4

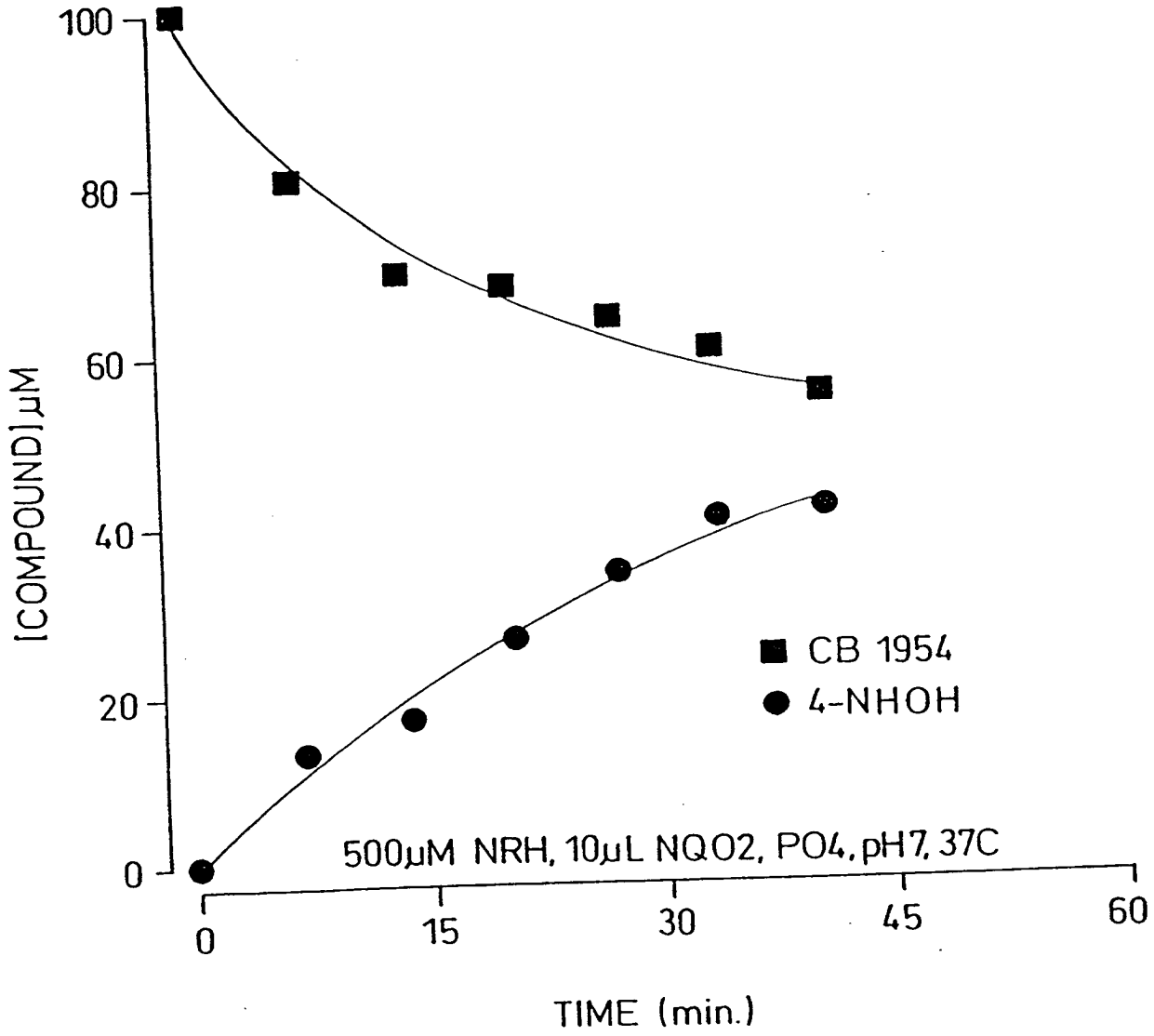
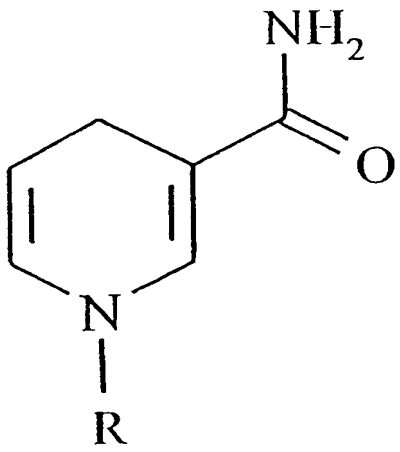

100
80
60
40
20
0
[COMPOUND] µM
CB 1954
4-NHOH
500µM NRH, 10µL NQO2, PO4, pH7, 37C
0
15
30
45
60
TIME (min.)

Fig. 5

B

```
ATGGCAGGTAAGAAAGTACTCATTGTCTATGCACACCAGGAACCCAAGTCTTTCAACGGATCCTTGAAGA   245
M  A  G  K  K  V  L  I  V  Y  A  H  Q  E  P  K  S  F  N  G  S  L  K  N

ATGTGGCTGTAGATGAACTGAGCAGGCAGGGCTGCACCGTCACAGTGTCTGATTTGTATGCCATGAACTT   315
 V  A  V  D  E  L  S  R  Q  G  C  T  V  T  V  S  D  L  Y  A  M  N  F     4

TGAGCCGAGGGCCACAGACAAAGATATCACTGGTACTCTTTCTAATCCTGAGGTTTTCAATTATGGAGTG   385
 E  P  R  A  T  D  K  D  I  T  G  T  L  S  N  P  E  V  F  N  Y  G  V    70

GAAACCCACGAAGCCTACAAGCAAAGGTCTCTGGCTAGCGACATCACTGATGAGCAGAAAAAGGTTCGGG   455
E  T  H  E  A  Y  K  Q  R  S  L  A  S  D  I  T  D  E  Q  K  K  V  R  E

AGGCTGACCTAGTGATATTTCAGTTCCCGCTGTACTGGTTCAGCGTGCCGGCCATCCTGAAGGGCTGGAT   525
 A  D  L  V  I  F  Q  F  P  L  Y  W  F  S  V  P  A  I  L  K  G  W  M    11

GGATAGGGTGCTGTGCCAGGGCTTTGCCTTTGACATCCCAGGATTCTACGATTCCGGTTTGCTCCAGGGT   595
 D  R  V  L  C  Q  G  F  A  F  D  I  P  G  F  Y  D  S  G  L  L  Q  G   140

AAACTAGCGCTCCTTTCCGTAACCACGGGAGGCACGGCCGAGATGTACACGAAGACAGGAGTCAATGGAG   665
K  L  A  L  L  S  V  T  T  G  G  T  A  E  M  Y  T  K  T  G  V  N  G  D     1

ATTCTCGATACTTCCTGTGGCCACTCCAGCATGGCACATTACACTTCTGTGGATTTAAAGTCCTTGCCCC   735
 S  R  Y  F  L  W  P  L  Q  H  G  T  L  H  F  C  G  F  K  V  L  A  P    18

TCAGATCAGCTTTGCTCCTGAAATTGCATCCGAAGAAGAAAGAAAGGGGATGGTGGCTGCGTGGTCCCAG   805
Q  I  S  F  A  P  E  I  A  S  E  E  E  R  K  G  M  V  A  A  W  S  Q      210

AGGCTGCAGACCATCTGGAAGGAAGAGCCCATCCCCTGCACAGCCCACTGGCACTTCGGGCAATAACT   873
R  L  Q  T  I  W  K  E  E  P  I  P  C  T  A  H  W  H  F  G  Q  <      231
```

Fig. 6



Compound number	R
1	$-CH_2CH_2CH_2SO_3^-$
2	$-CH_2CONH_2$
3	$-CH_2CH_2CH_3$
4	$-CH(CH_3)_2$
5	$-CH_2CH_2CH_2OH$
6	$-CH_2CH_2OH$
7	$-CH_2CH_2COOH$
8	$-CH_2C_6H_5$
9	$-CH_3$
10	$-CH_2CH_3$
11	$-CH_2CH_2C_6H_5$

Fig. 7

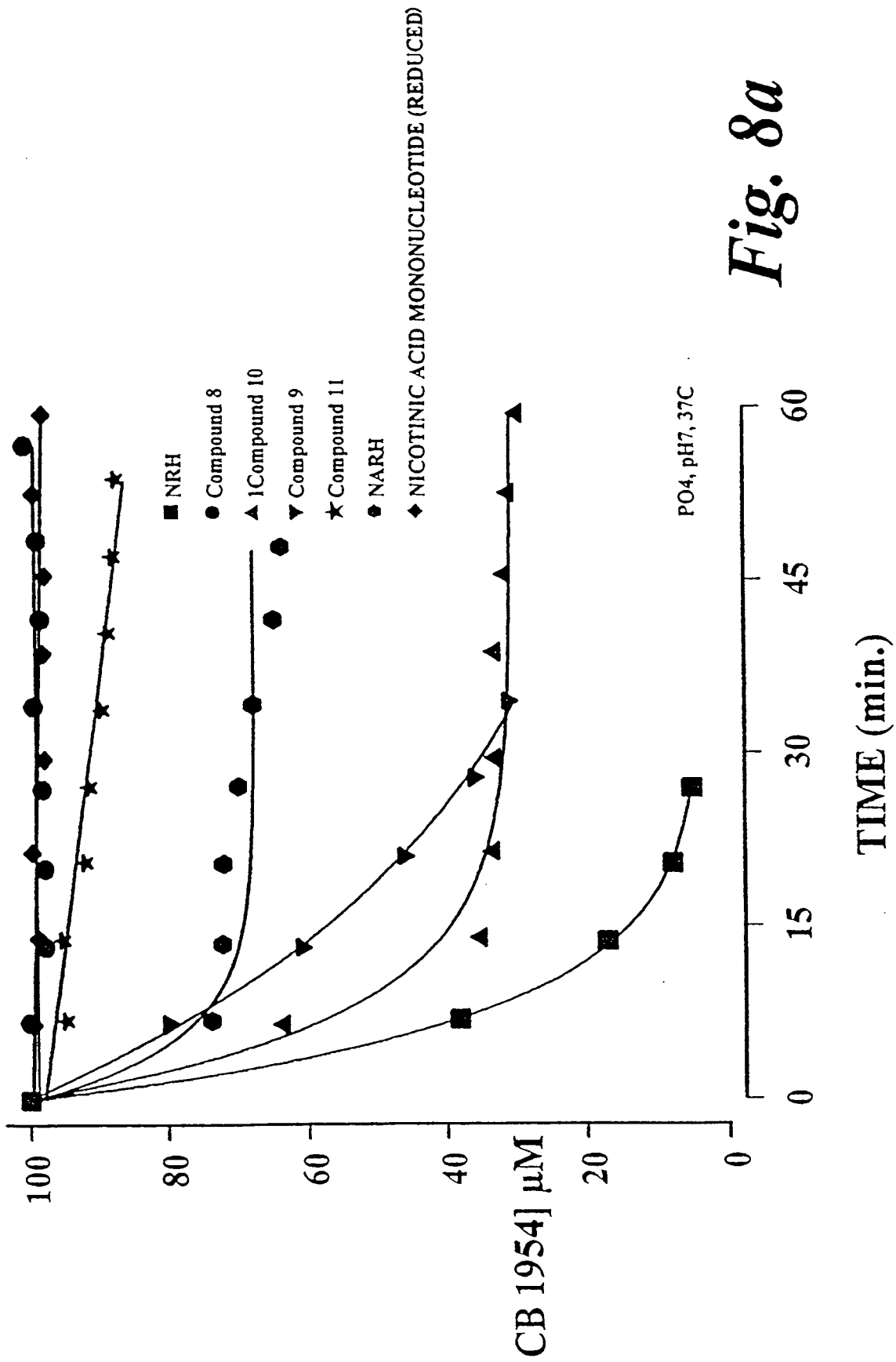


Fig. 8a

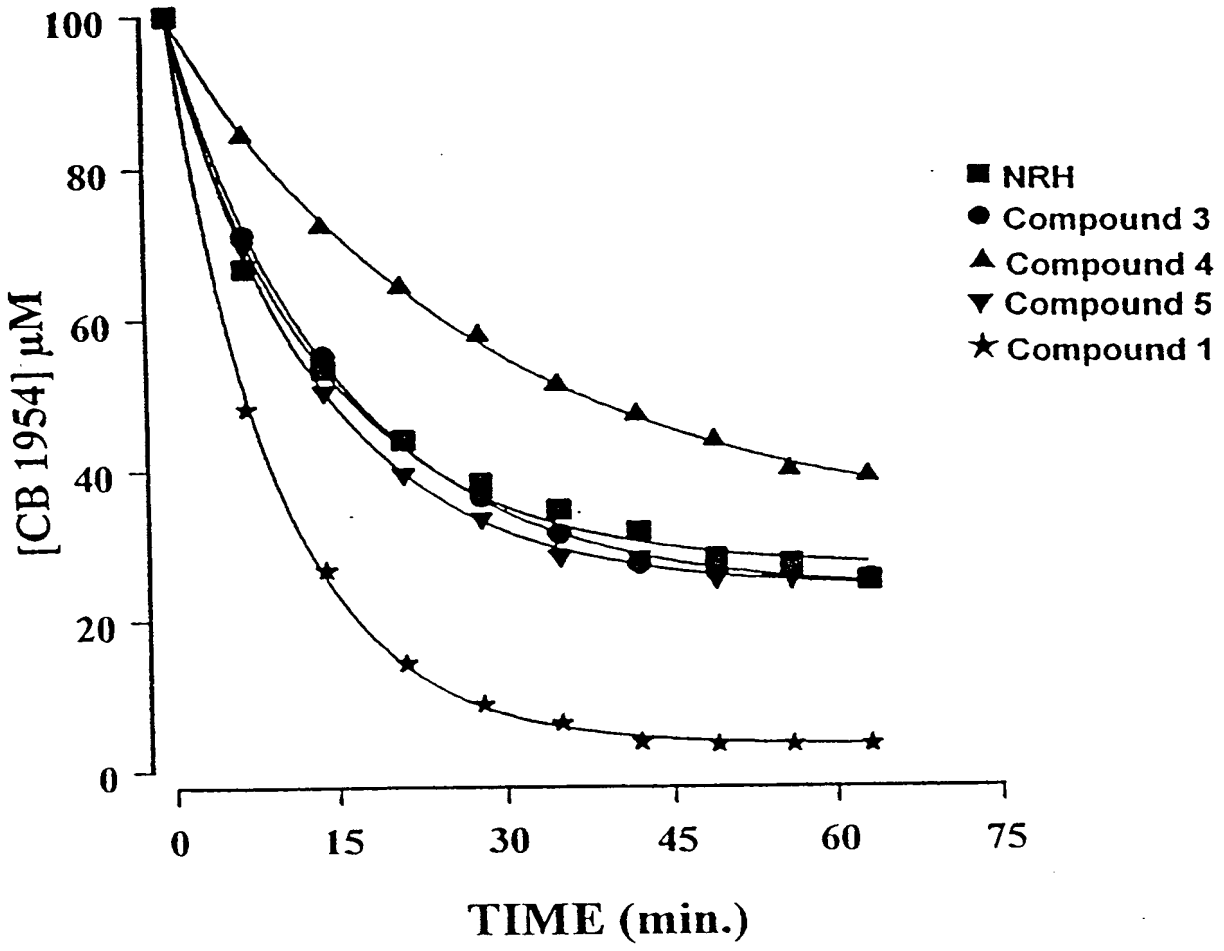


Fig. 8b

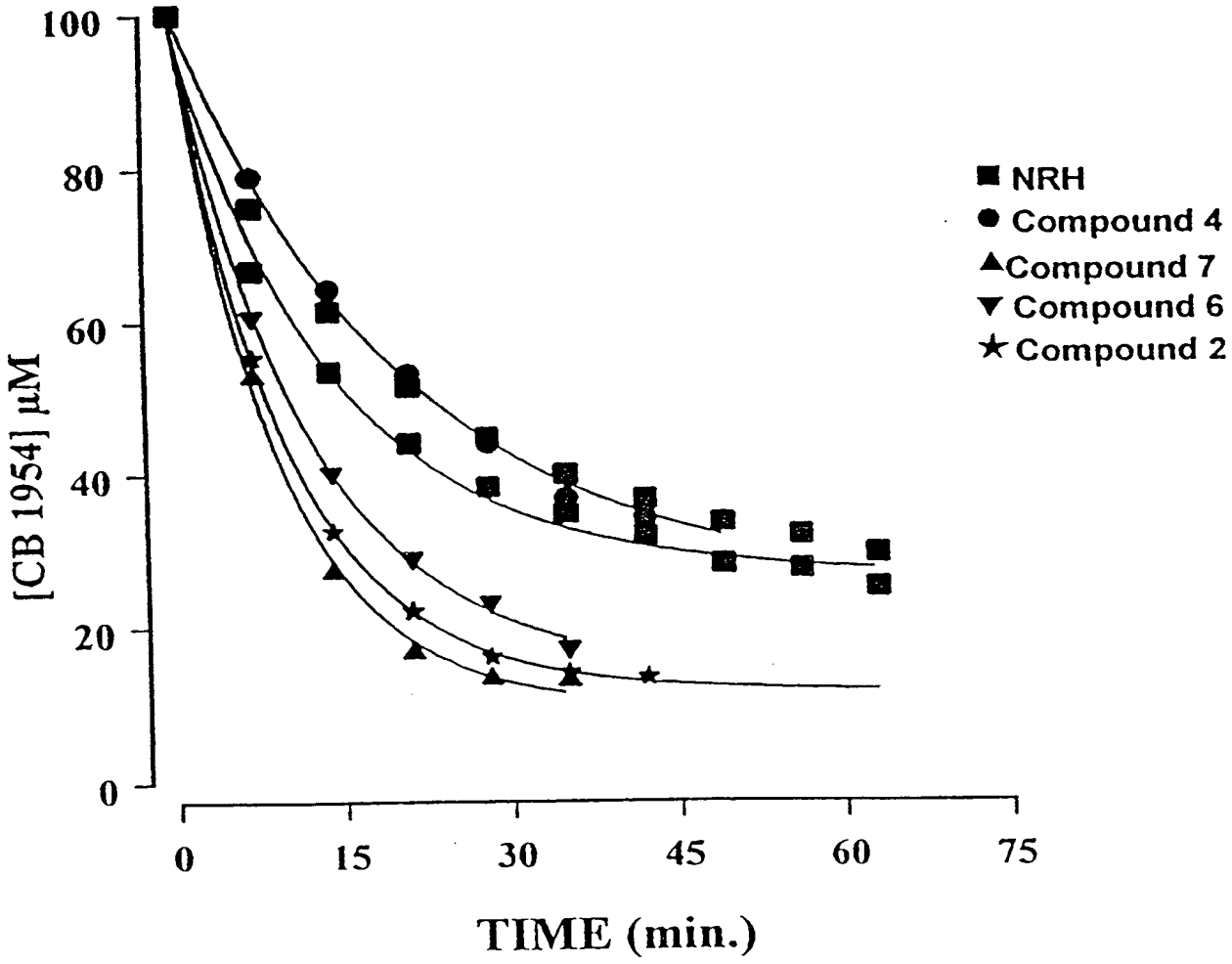

100
80
60
40
20
0
[CB 1954] µM
0
15
30
45
60
75
TIME (min.)
NRH
Compound 4
Compound 7
Compound 6
Compound 2

Fig. 8c

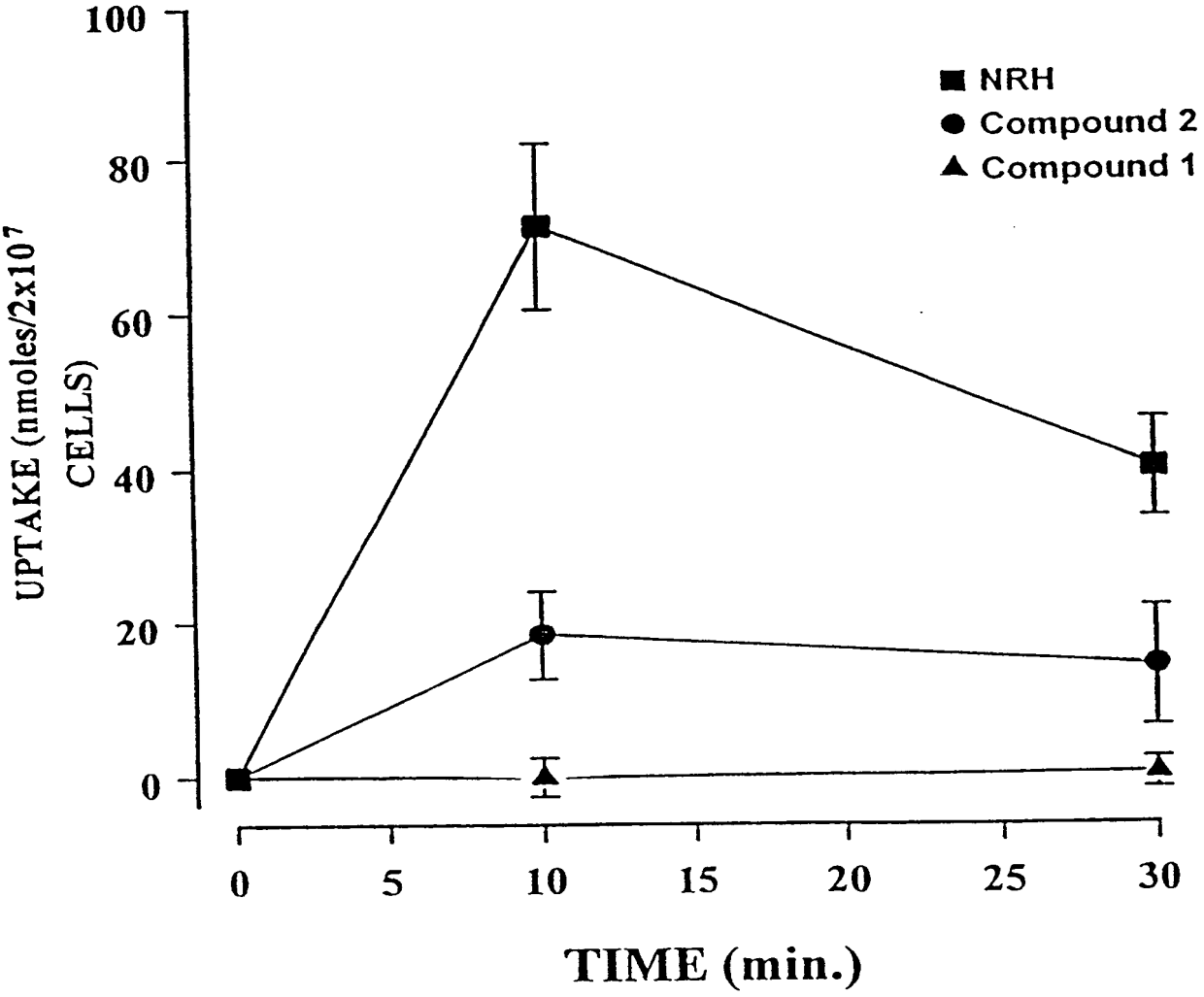

100
80
60
40
20
0
UPTAKE (nmoles/2x10⁷ CELLS)
NRH
Compound 2
Compound 1
0
5
10
15
20
25
30
TIME (min.)

Fig. 9

11/19

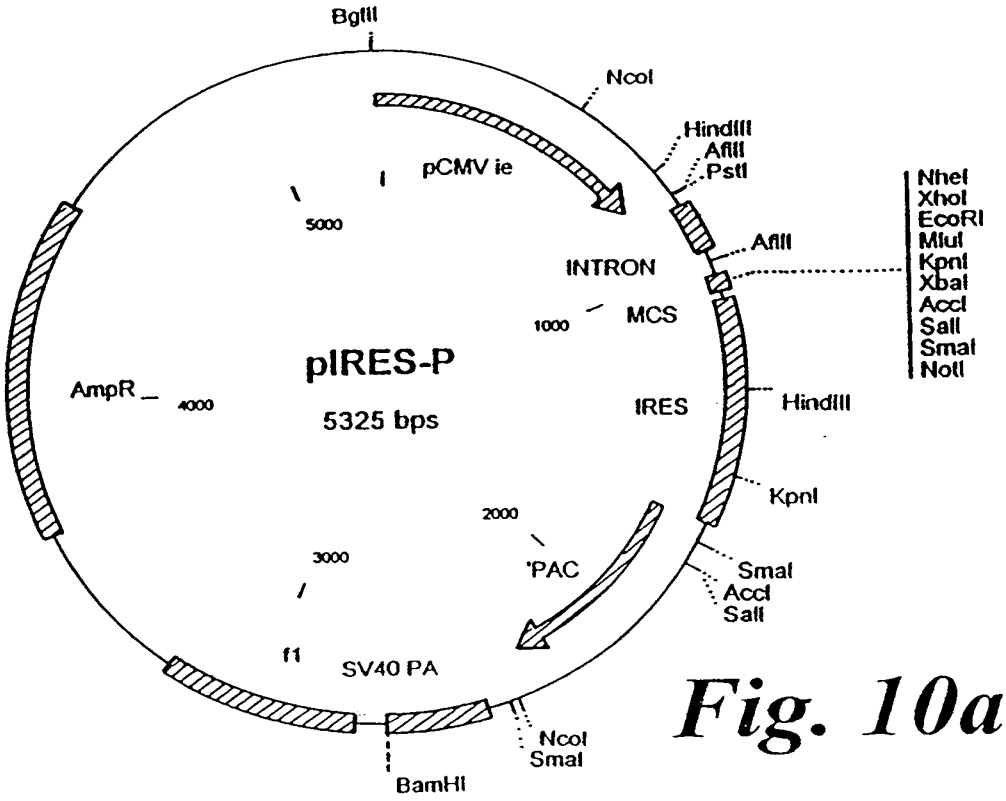


Fig. 10a

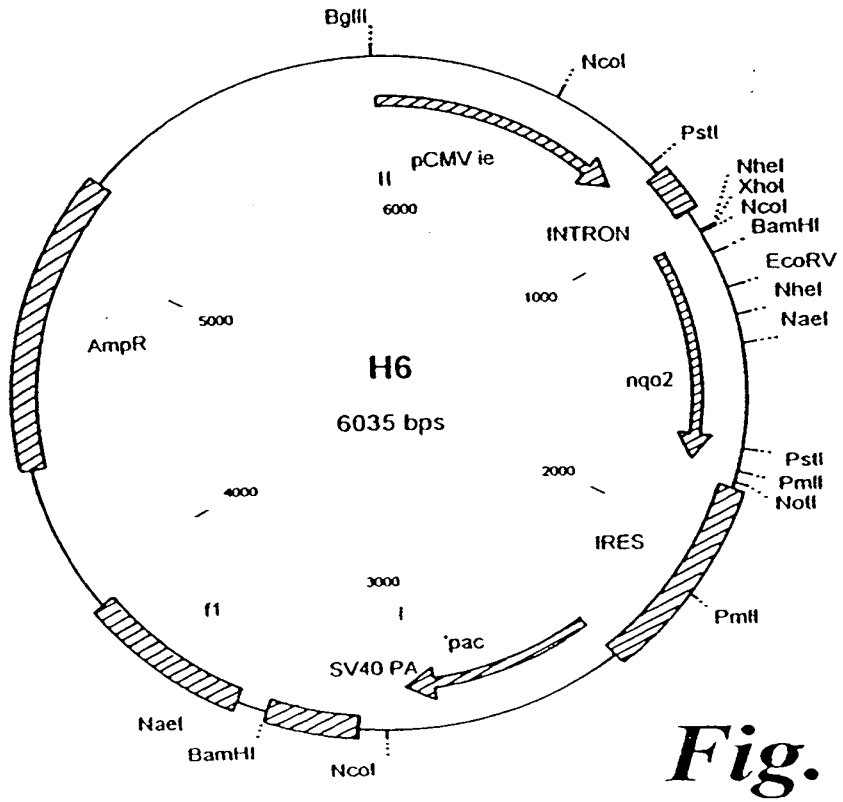


Fig. 10b

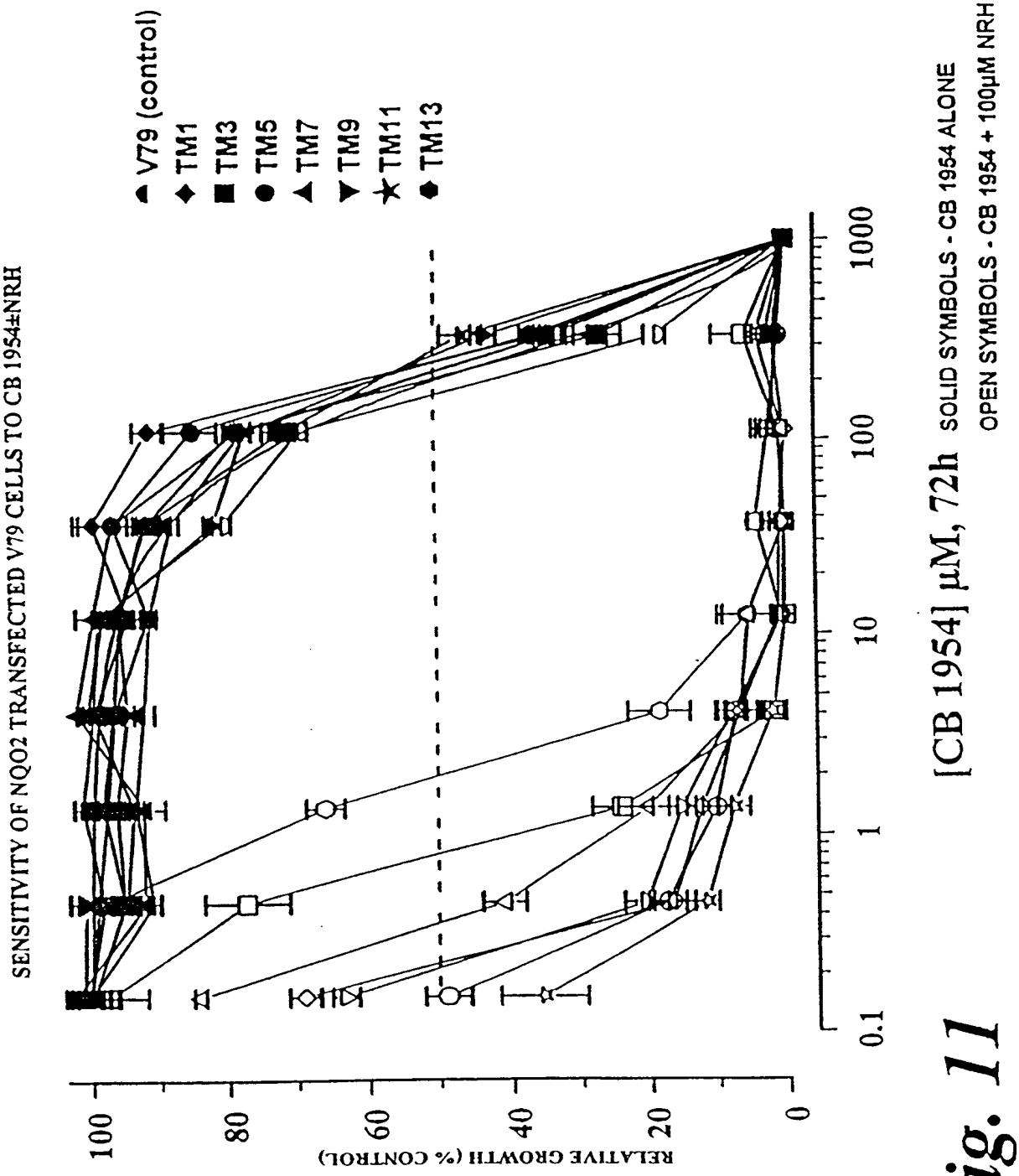

V79 (control)
TM1
TM3
TM5
TM7
TM9
TM11
TM13
SENSITIVITY OF NQO2 TRANSFECTED V79 CELLS TO CB 1954±NRH
RELATIVE GROWTH (% CONTROL)
100
80
60
40
20
0
0.1
1
10
100
1000
[CB 1954] µM, 72h
SOLID SYMBOLS - CB 1954 ALONE
OPEN SYMBOLS - CB 1954 + 100µM NRH

Fig. 11

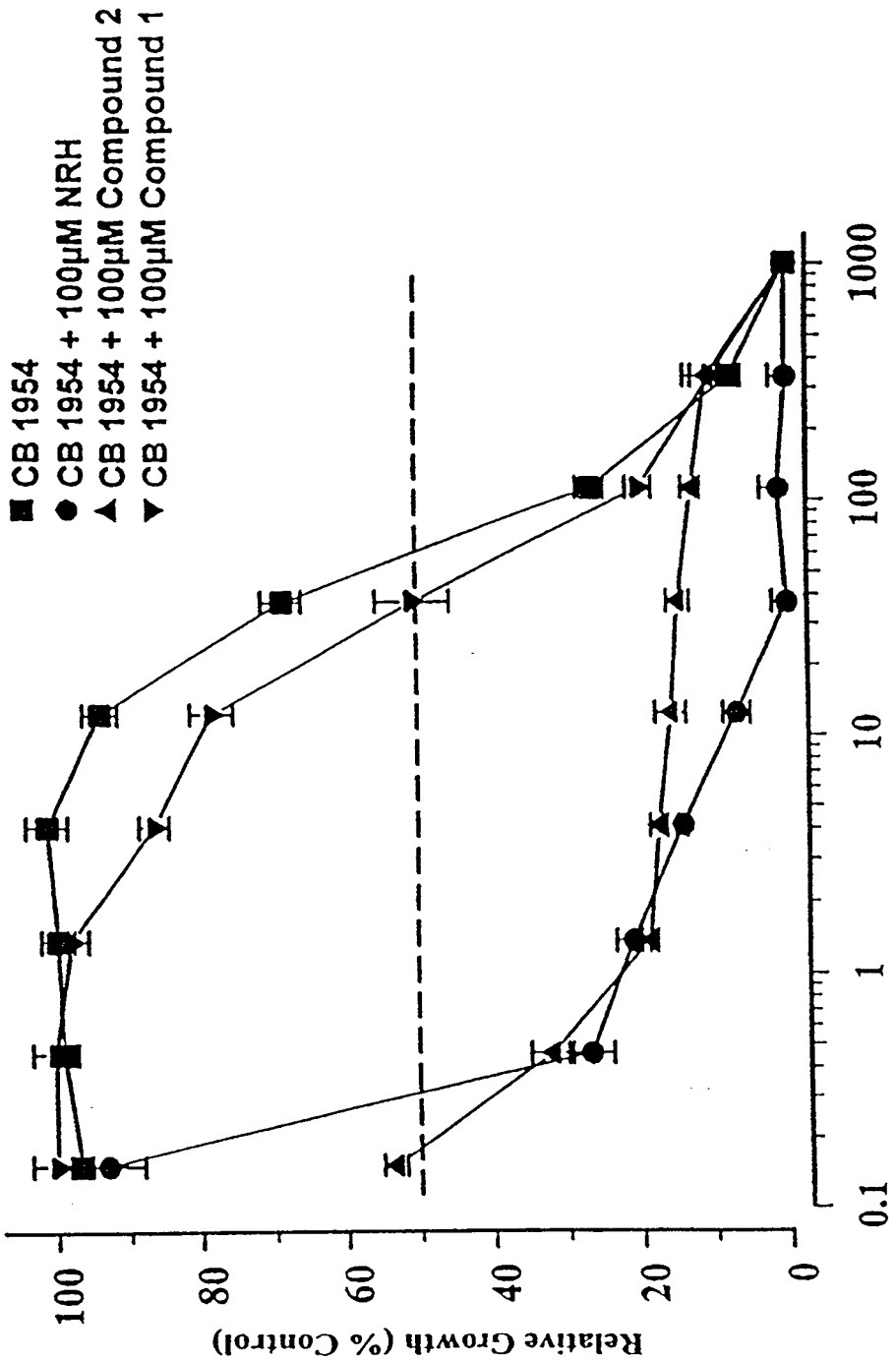

CB 1954
CB 1954 + 100µM NRH
CB 1954 + 100µM Compound 2
CB 1954 + 100µM Compound 1
Relative Growth (% Control)
0
20
40
60
80
100
0.1
1
10
100
1000
[CB 1954] µM, 144h

Fig. 12

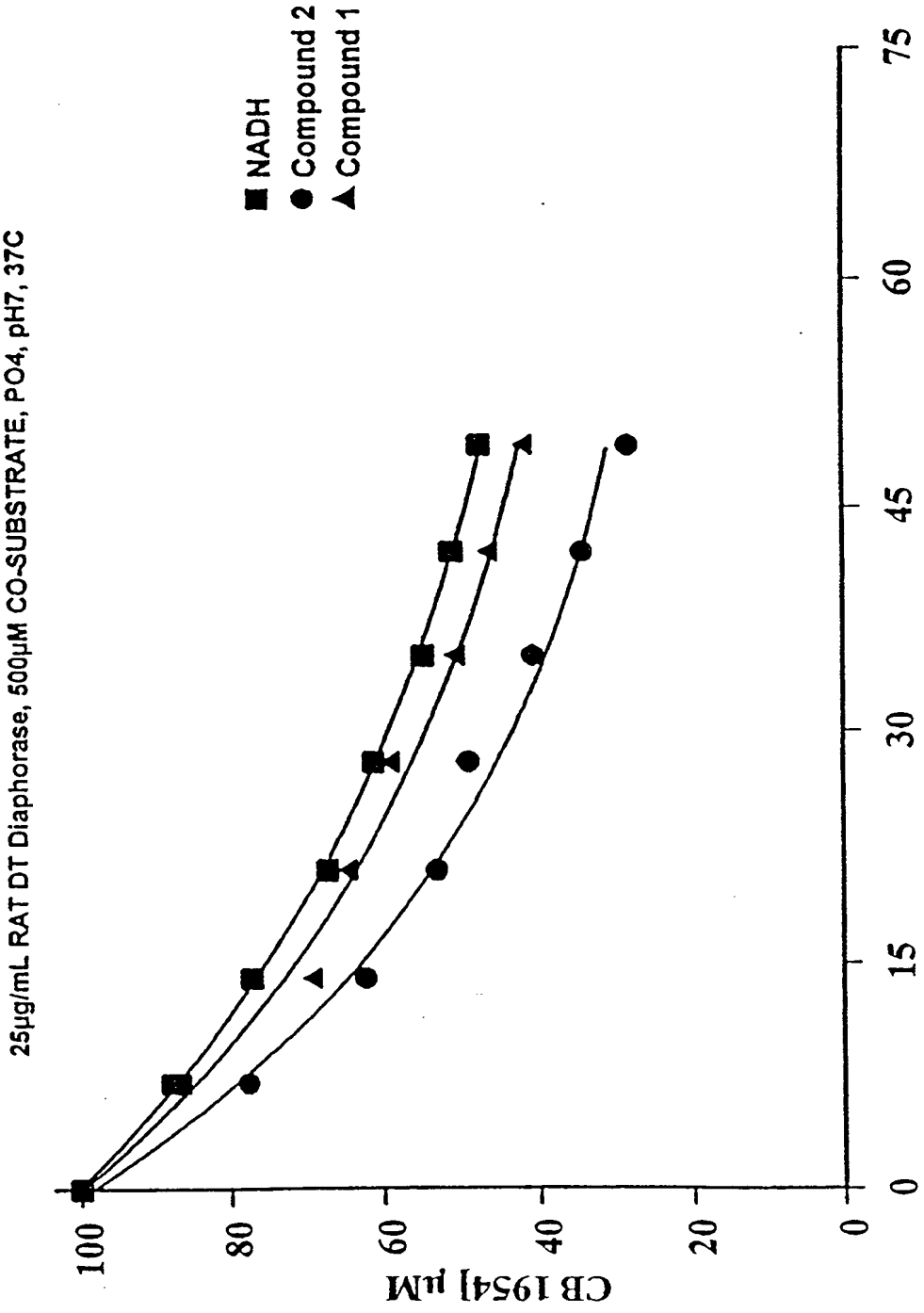

NADH
Compound 2
Compound 1
25µg/mL RAT DT Diaphorase, 500µM CO-SUBSTRATE, PO4, pH7, 37C
CB 1954] µM
100
80
60
40
20
0
0
15
30
45
60
75
TIME (min.)

Fig. 13

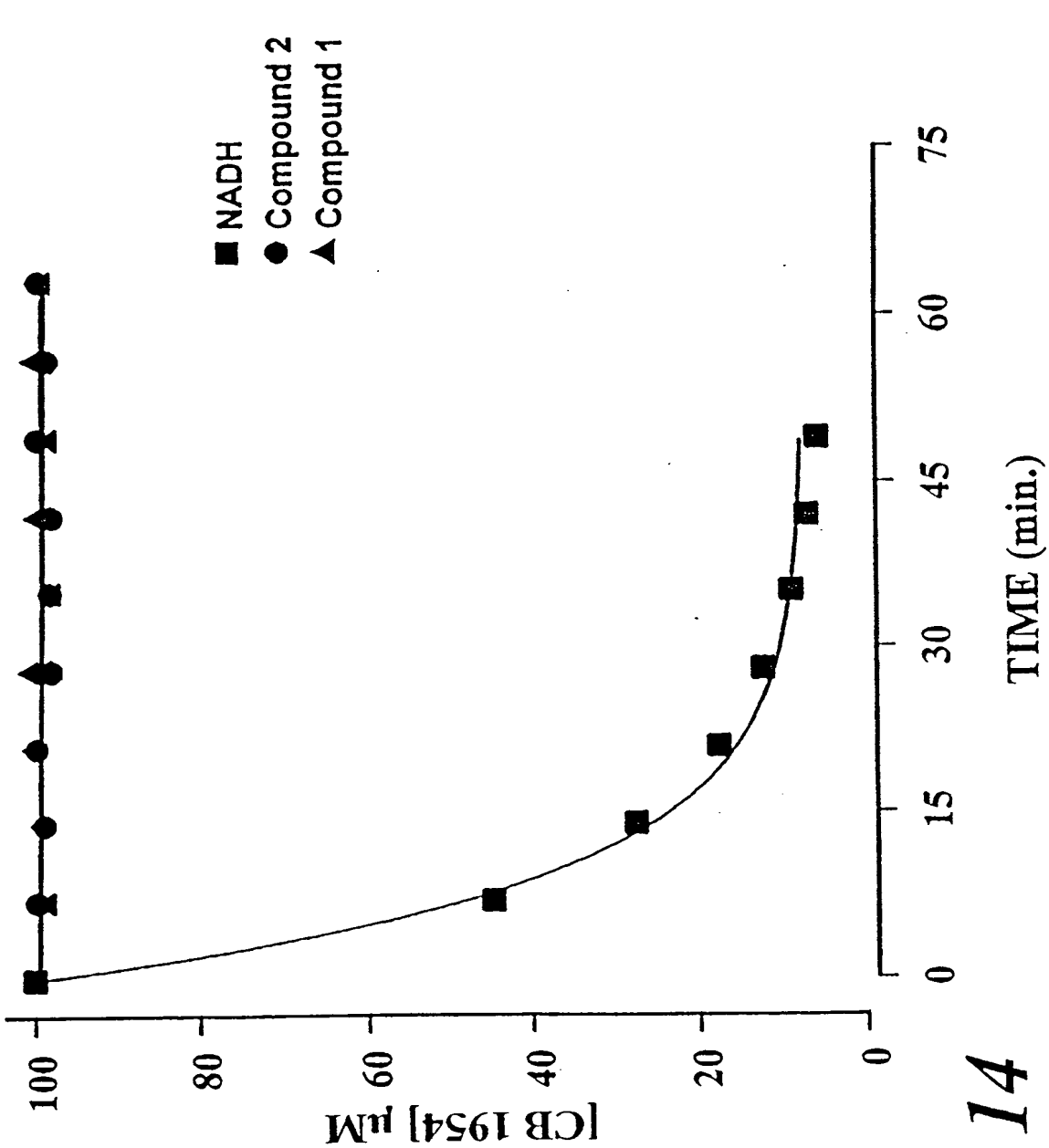

0.5µg/mL Nitroreductase, 500µM CO-SUBSTRATE, PO4, pH7, 37C
NADH
Compound 2
Compound 1
[CB 1954] µM
100
80
60
40
20
0
0
15
30
45
60
75
TIME (min.)

Fig. 14

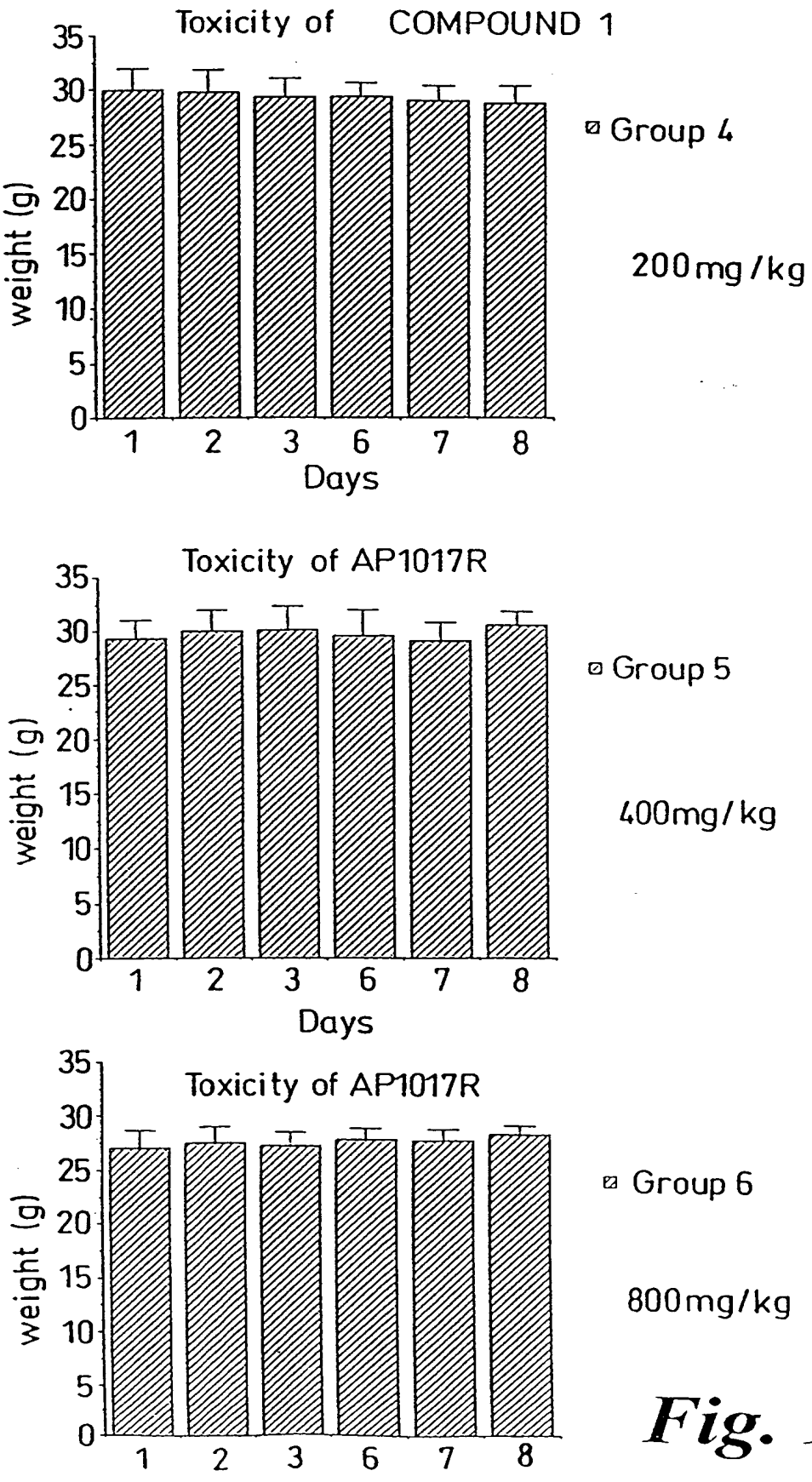
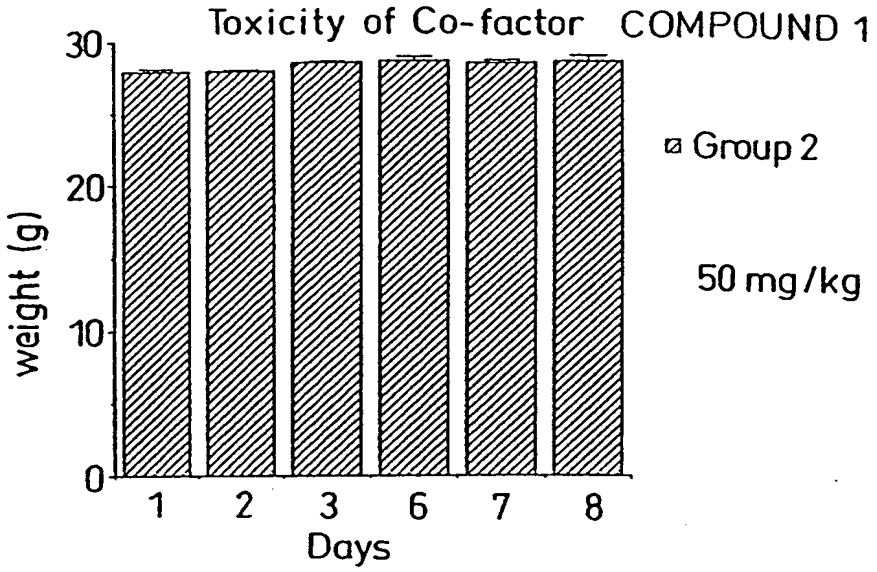
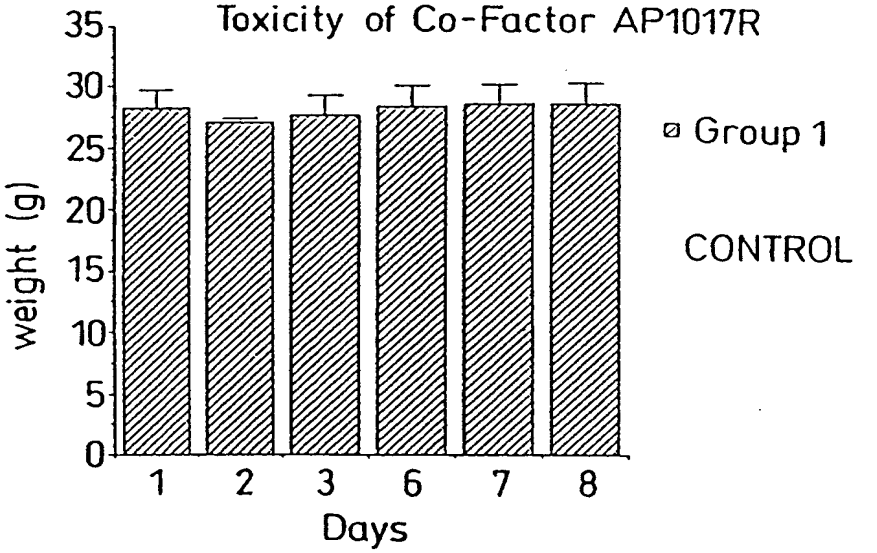

Toxicity of COMPOUND 1
weight (g)
35
30
25
20
15
10
5
0
1 2 3 6 7 8
Days
Group 4
200mg/kg
Toxicity of AP1017R
weight (g)
Days
Group 5
400mg/kg
Toxicity of AP1017R
weight (g)
Group 6
800mg/kg

Fig. 15


Toxicity of Co-factor COMPOUND 1
weight (g)
30
20
10
0
1 2 3 6 7 8
Days
Group 2
50 mg/kg


Toxicity of Co-Factor AP1017R
weight (g)
35
30
25
20
15
10
5
0
1 2 3 6 7 8
Days
Group 1
CONTROL

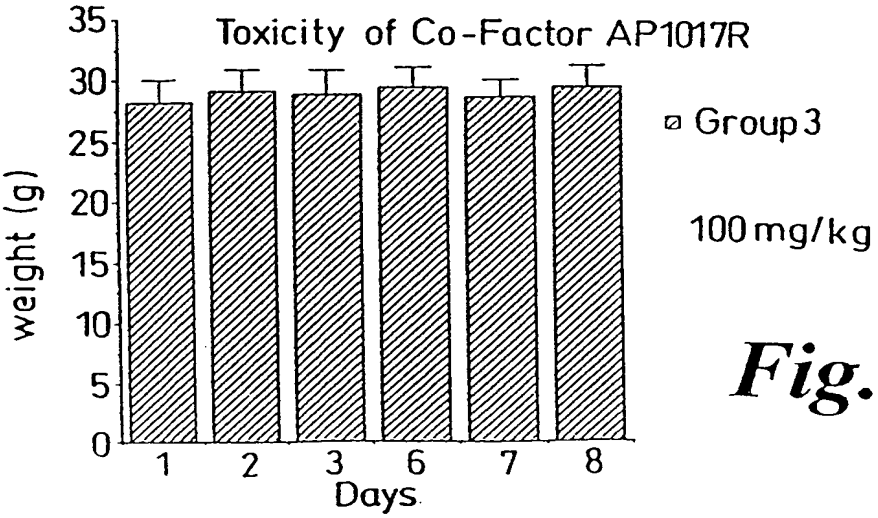

Toxicity of Co-Factor AP1017R
weight (g)
35
30
25
20
15
10
5
0
1 2 3 6 7 8
Days
Group 3
100 mg/kg

Fig. 16

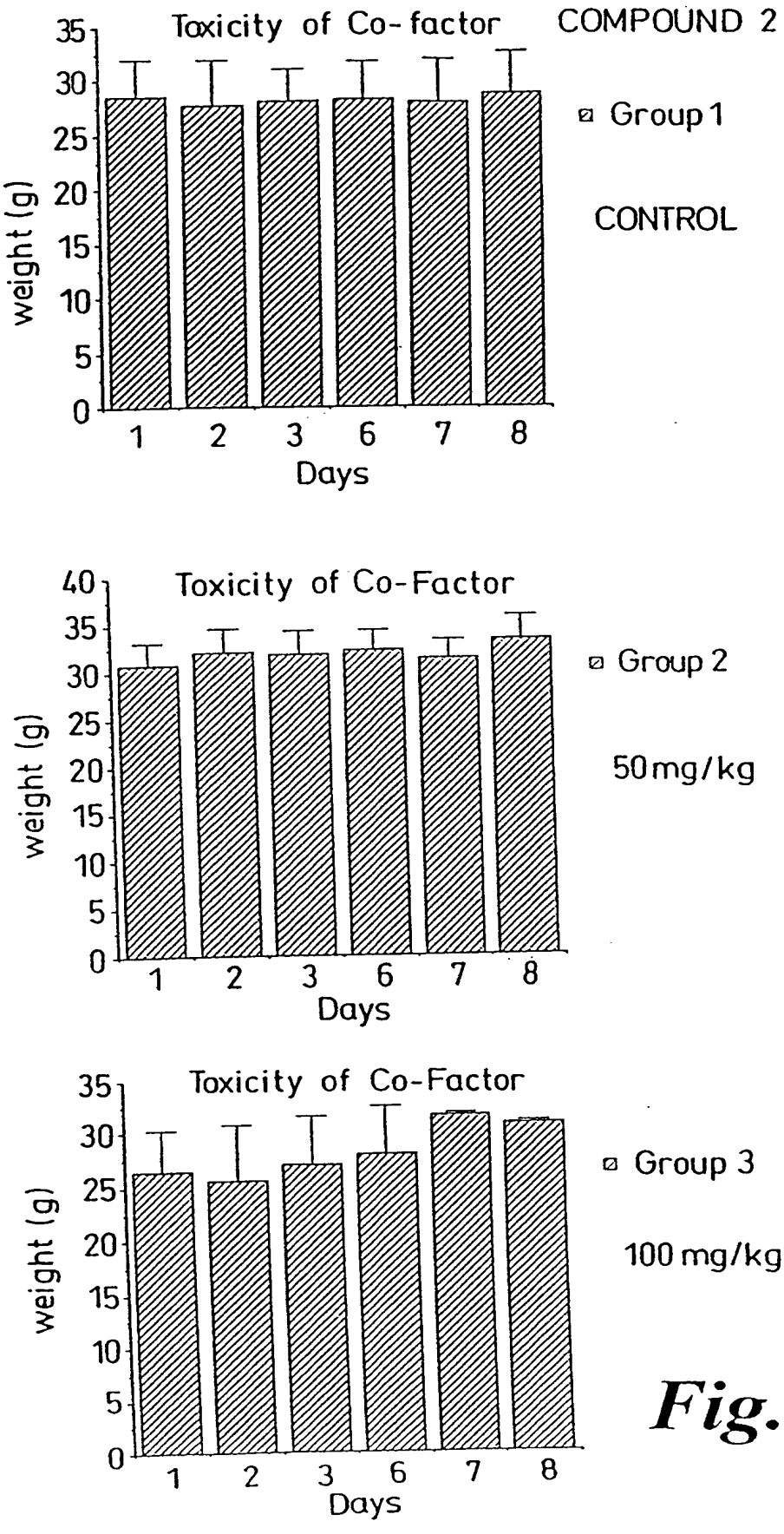

Toxicity of Co-factor
COMPOUND 2
weight (g)
Days
Group 1
CONTROL
Toxicity of Co-Factor
Group 2
50mg/kg
Toxicity of Co-Factor
Group 3
100 mg/kg

Fig. 17

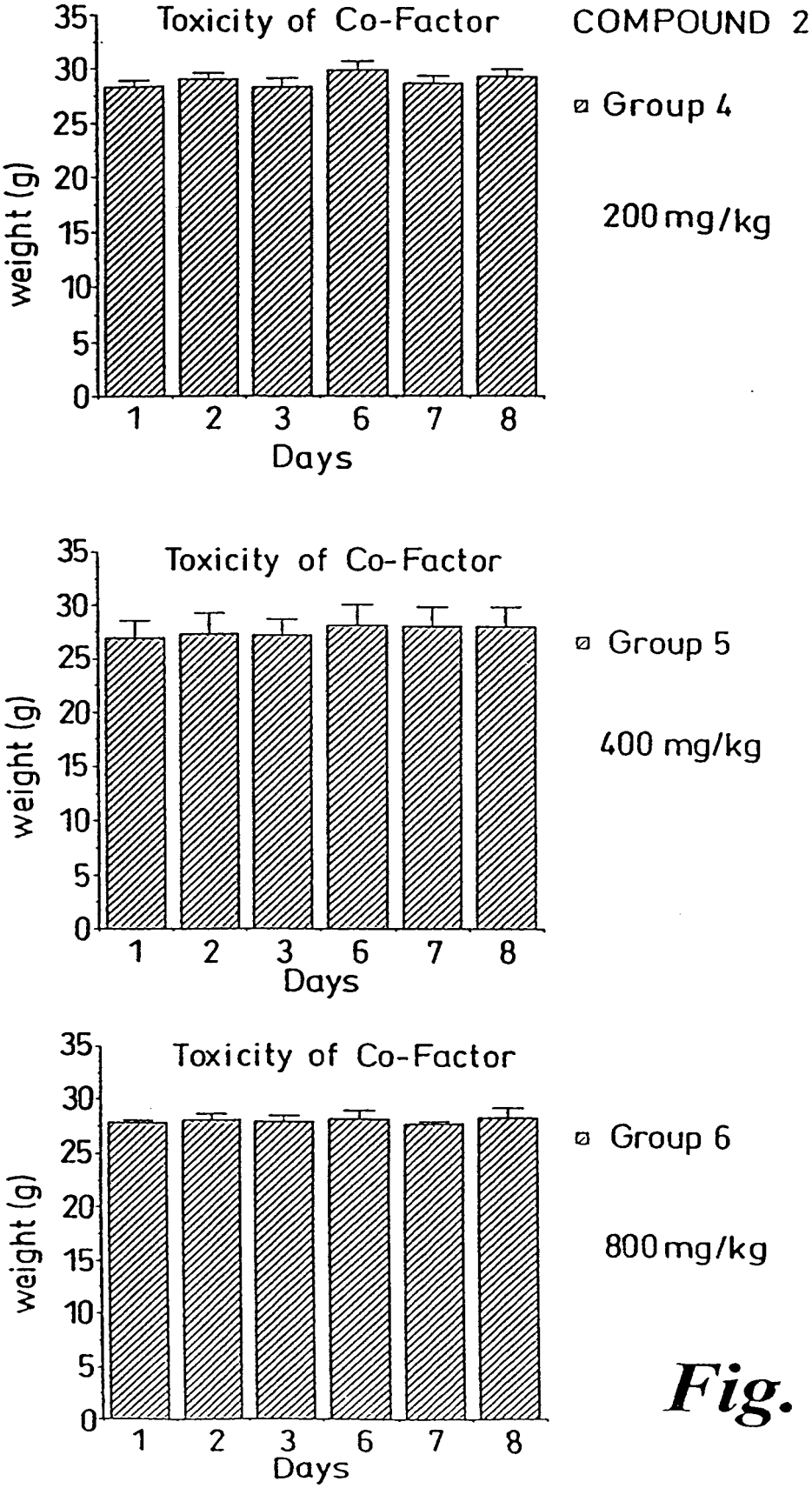

Toxicity of Co-Factor
COMPOUND 2
weight (g)
35
30
25
20
15
10
5
0
1 2 3 6 7 8
Days
Group 4
200 mg/kg
Toxicity of Co-Factor
weight (g)
Days
Group 5
400 mg/kg
Toxicity of Co-Factor
weight (g)
Days
Group 6
800 mg/kg

Fig. 18